Docket No.: 616292000111
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of:
David C. BAULCOMBE et al.

Application No.: 10/805,804

Filed: March 22, 2004

For: GENE SILENCING

Confirmation No.: 9959

Art Unit: 1638

Examiner: Ashwin D. Mehta, Ph.D.

BRIEF ON APPEAL

MS Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Madam:

A Notice of Appeal was filed in the present application on 6 November 2008, along with a Pre-Appeal Brief Request for Review. A decision stating that there were still appealable issues with respect to the appealed claims 116-130 was mailed 2 December 2008. Thus, the due date for filing of a Brief remained 6 January 2009. A petition for an extension of time of two (2) months until 6 March 2009 is enclosed along with the required fee. **This application was made special and expedited handling is respectfully requested.** Appellants respectfully request that the bases for rejection as to the appealed claims 116-130 be withdrawn and these claims passed to issue.

1. Real Party in Interest

The Real Party in Interest is the assignee herein, Plant Biosciences Limited (PBL) a United Kingdom entity. PBL is an independent technology and intellectual property management company specializing in life sciences.

2. Related Appeals and Interferences

There are no interferences or judicial proceedings known to appellants, appellants' legal representative or assignee which may be related to, directly affect, or be directly affected by or have a bearing on the Board's decision in this case. However, one copending application in this family has a Notice of Appeal of record. A Notice of Appeal has been filed in Serial No. 11/013,316;.

3. Status of Claims

Claims 1-115 have been canceled. Claims 116-130 have been finally rejected and are on appeal.

4. Status of Amendments

No amendments to the claims were proposed after final rejection.

5. Summary of Claimed Subject Matter

The claims are directed to a method of silencing a gene in cells by post-transcriptional gene silencing (page 3, lines 4-6, in combination with page 2, lines 13-14, page 9, lines 32-34) which method uses short RNA molecules (SRMs) (page 3, lines 10-13). These SRMs are isolated short sense RNA molecules (SSRMs) and isolated short antisense RNA molecules (SARMs) which are supplied at the same abundance (page 2, lines 12-20 and page 23, lines 35-40) which have any number of nucleotides between 20 and 30 including 20-24 (page 4, lines 4-14, and page 4, lines 20-24). The SARMs are complementary to a region of the target RNA transcribed from the

gene which is silenced and the SSRMs correspond to the target RNA (page 2, lines 19-20 and 30-33). Alternatively, it could be stated that said SARMs base pair with a target RNA (page 2, lines 30-33). These SRMs may be produced intracellularly by virtue of a construct which produces them (page 10, lines 7-11).

Thus, the various features of the independent claims are supported by the specification as indicated below.

116. A method of silencing a gene in cells by post-transcriptional gene silencing (PTGS) (page 3, lines 4-6 combined with page 2, lines 13-14, page 9, lines 32-34) which method comprises introducing into said cells a composition that contains short RNA molecules (SRMs) (page 3, lines 10-13),

which SRMs are isolated short sense RNA molecules (SSRMs) and isolated short antisense RNA molecules (SARMs) at the same abundance (page 2, lines 12-20 and page 23, lines 35-40);

wherein said SARMs are complementary to a region of a target RNA transcribed from a gene which is silenced when said short RNA molecules are present in cells containing said gene and said SSRMs correspond to said target RNA(page 2, lines 19-20 and 30-33); and

wherein the SSRMs and SARMs consist of 20, 21, 22, 23 or 24 nucleotides (page 4, lines 4-14 and 20-24),

whereby said gene is silenced.

120. A method of silencing a gene in cells of an organism by post-transcriptional gene silencing (PTGS) (page 3, lines 4-6 combined with page 2, lines 13-14, page 9, lines 32-34) which method comprises introducing into said cells a composition that contains isolated short antisense RNA molecules (SARMs) and isolated short sense RNA molecules (SSRMs) corresponding to a target RNA transcribed from said gene (page 2, lines 12-20), the nucleotide sequences of which consist of 20, 21, 22, 23 or 24 nucleotides (page 4, lines 4-14 and 20-24) and wherein said SARMs can base pair with said target RNA (page 2, lines 12-20).

125. A method of silencing a gene in cells by post-transcriptional gene silencing (PTGS) (page 3, lines 4-6 combined with page 2, lines 13-14, page 9, lines 32-34) which method comprises introducing into said cells a composition that contains at least one vector that, when introduced into said cells, produces short RNA molecules (SRMs) (page 10, lines 7-11),

which SRMs are short sense RNA molecules (SSRMs) and short antisense RNA molecules (SARMs) (page 3, lines 10-13);

wherein said SARMs are complementary to a region of a target RNA transcribed from a gene which is silenced when said short RNA molecules are present in cells containing said gene and said SSRMs correspond to said target RNA (page 2, lines 12-20); and

wherein the SSRMs and SARMs consist of 20, 21, 22, 23 or 24 nucleotides (page 4, lines 4-14 and 20-24),

whereby said gene is silenced.

128. A method of silencing a gene in cells of an organism by post-transcriptional gene silencing (PTGS) (page 3, lines 4-6 combined with page 2, lines 13-14, page 9, lines 32-34) which method comprises introducing into said cells a composition that contains at least one vector that, when introduced into said cells, produces (page 10, lines 7-11) short antisense RNA molecules (SARMs) and short sense RNA molecules (SSRMs) corresponding to a target RNA transcribed from said gene (page 2, lines 12-20), the nucleotide sequences of which consist of 20, 21, 22, 23 or 24 nucleotides (page 4, lines 4-14 and 20-24) and wherein said SARMs can base pair with said target RNA (page 2, lines 12-20).

Appellants do not wish the rather technical and formal Summary of the Invention to obscure the nature of the contribution of the present inventors. As argued on page 5 of the Response filed 29 September 2008 to the final Rejection, none of the authors of the cited documents made the basis of rejection herein understood that it is short RNA molecules that mediate gene silencing by PTGS. There was no understanding in the art that such short molecules mediate this silencing. Attached to

that Response were exhibits demonstrating that Dr. Baulcombe had been awarded both the Lasker Prize and the Franklin Institute Medal in Life Science for the discovery that lies at the basis of the claimed invention herein. These exhibits are enclosed in the Evidence Appendix.

Briefly, the art considered PTGS to be mediated by long strands of double-stranded RNA in systems in general, including nematodes, the organism in which this was established. Fire and Mello, two of the inventors on the cited Fire patent, were awarded the Nobel prize for this very discovery. Until the work of the present inventors established the presence of both sense and antisense short RNA's in plants undergoing PTGS silencing, it was understood that such silencing required much larger RNA molecules. That is why the Lasker Prize and the Franklin Medal were awarded to Baulcombe.

6. Grounds of Rejection to be Reviewed on Appeal

All of the outstanding rejections are made over the art. They are as follows.

1. Claims 125-130 were rejected under 35 U.S.C. § 102(e) over Graham (U.S. 6,573,099). There is no rejection of claims 116-124 over Graham alone.
2. Claims 116-124 were rejected as obvious over Fire (U.S. 6,506,559) in view of Graham. Claims 125-130 were not included in this rejection.
3. Claims 116-130 were rejected as obvious over Brown (U.S. 6,723,897).

7. Argument

A. Graham does not meet the standard of anticipation required in order to defeat claims 125-130.

Claims 125-130 all require constructs that produce short RNA molecules (SRMs) that *consist of* 20-24 nucleotides. The Examiner is unable to point to any portion of Graham that discusses the length of RNA molecules produced. Graham only discusses a sequence or length in

terms of DNA contained in Graham's vectors, never any length of any RNA produced by such vectors.

Even if the "structural genes" contained in Graham's synthetic genes were disclosed to contain only 20-30 nucleotides, as the Examiner asserts (and appellants dispute, see discussion below), this does not necessarily result in RNA transcripts having this same length. It is well known in the art that RNA transcripts typically include, for example, polyadenylation signals and polyA itself, as is described in standard molecular biology textbooks. This would extend the length of the RNA transcript beyond the length of the structural gene component. If it is the position of the Examiner that constructs described by Graham that putatively contain structural gene components of 20-30 nucleotides inherently produce RNA molecules of this length, this position is not supportable as inherency would be present only if such RNA were an inevitable result of the vector constructs. Thus, in order to anticipate, at a minimum, generation of sequences of this length by the constructs described by Graham must be a certain and consistent result of expression. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991). This cannot be the case, since it is known that sequence additional to that in the sequence intended to be transcribed may be present.

Thus, the situation here is similar to that in *Net MoneyIn, Inc. v. VeriSign, Inc.,* 545 F3d 1359, (Fed. Cir. 2008) where a claim to a sequence of steps requiring five elements was found not to be anticipated even though all five elements were contained within the cited document. In order to obtain the sequence of steps or "arrangement" set forth in the claim, elements from two different sequences of steps needed to be combined. As the Court stated, a prior art reference, in order to anticipate under 35 U.S.C. § 102 must not only disclose all of the elements of the claims

within the four corners of the document but must also disclose those elements "arranged as in the claim" citing *Connell v. Sears Roebuck & Co.*, 722 F2d 1542, 1548, 220 USPQ 193 (Fed. Cir. 1983).

Here, the Examiner has combined a number asserted to be associated with a structural gene component of a synthetic gene with another category of nucleic acid molecules – the RNA produced. The RNA produced will not necessarily be limited to the nucleotides transcribed directly from the structural gene component. As was the case in *Net MoneyIn*, the elements of the claim are not arranged in the cited document as they are in the claim. Claims 125-130 of the present application do not stipulate the length of any structural genes or DNA sequences in the claimed constructs, but rather require that the constructs "produce" short RNA molecules of specified lengths of 20-24 nucleotides. This is nowhere described in Graham.

In addition to the disconnect between definition of the RNA produced and the DNA contained in a construct producing it, it has been and continues to be asserted by appellants that there is a minimum required size of a structural gene sequence included in the Graham constructs that is taught, but ignored by the Examiner. At column 5, lines 9-15 Graham states:

> the only **requirement** being that the synthetic gene is substantially identical at the nucleotide sequence level to at least a part of the target gene, the expression of which is to be modified. By "substantially identical" is meant that the structural gene sequence of the synthetic gene is at least about 80%-90% identical to **30 or more contiguous nucleotides of the target gene**... .

This explicit teaching is reiterated at column 6, lines 18-24. This explicit teaching of the **requirements** of the Graham construct has been given no weight by the Examiner, who continues to assert that the disclosure at column 6, lines 25-40, (which discusses preferred structural gene

components in terms of nucleotide elements comprising at least about 20-30 nucleotides in length derived from specific viral DNA polymerase, viral RNA polymerase, viral coat protein or visually-detectable gene) somehow renders the requirements taught at column 5 and reiterated at column 6 null and void. At a minimum, these different sections of the Graham specification render it ambiguous as to the minimum size of even the DNA structural gene component included in the Graham construct.

The Examiner has never responded adequately to appellants' arguments, made, for example, on pages 11-12 of the Response filed 29 September 2008. Appellants there pointed out that Graham does not meet the legal standard for anticipation of a smaller range by a much larger one that contains it. This was cast in the Response in two ways:

(a) As a species *vs.* genus issue (a genus not even providing obviousness of a species that is not explicitly suggested by the document disclosing the genus, citing *In re Baird*, 16 F3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994)), and

(b) the legal criterion for anticipation of "range" as set forth in *Atofina v. Great Lakes Chem. Corp.*, 441 F3d 991, 78 USPQ2d 1417 (Fed. Cir. 2006). In *Atofina*, the reference taught a temperature range of 100-500°C and the claimed range of 350-450°C was held not to be anticipated.

Graham clearly teaches, even if the interpretation of Graham by the Examiner is conceded (which it is not), a broad range of 20-1,385 nucleotides. The upper number is exemplified by use of a full-length cDNA (column 16, line 55, and the construct in column 18, lines 27-37). Clearly Graham, by teaching constructs in the range of 20 to 1,385 nucleotides, cannot anticipate or even suggest the claimed range of 20-24 nucleotides.

Indeed, the lower numbers in Graham's range are actively taught away from. For example, Graham teaches an embodiment wherein

> [S]aid synthetic gene at least comprises multiple structural gene sequences wherein each of said structural gene sequences comprises a nucleotide sequence that is substantially identical to the nucleotide sequence of the target gene or a derivative thereof or a complementary sequence thereto and wherein the multiple structural gene sequences are placed operably under the control of a single promoter sequence. (Column 9, lines 55-64.)

Column 10 stipulates that the total length of the multiple structural gene sequence should be no more than, at a maximum, 500-2,000 bases. The relevant embodiment illustrated by Graham set forth in column 18 at lines 27-38, provides a construct with an inverted repeat or palindrome of a complete BEV polymerase open reading frame under the control of a single promoter. The reader would thus infer that longer sequences of identity with the target gene are preferable.

In summary, appellants thus assert, as discussed above, that the rejection of claims 125-130 for anticipation over Graham is in error for at least the following reasons:

1. Graham never discusses size of RNA produced, only the size of "structural genes", and transcription typically adds more nucleotides;
2. Graham teaches a minimum of 30 nucleotides is required for the structural gene; and
3. Graham teaches a large range of sizes for the structural gene and does not anticipate lengths of 20-24 nucleotides as a matter of law.

B. Claims 116-124 are Inventive Over Fire in Combination with Graham.

The predicate of the Examiner's position is that Fire teaches the use of RNA molecules as short as 25 nucleotides. This position is not supported by the disclosure of Fire. The only place in the Fire specification where 25 bases in RNA is mentioned, as has been repeatedly argued during

prosecution, for example, in Responses filed 28 September 2008 (page 13), on 2 May 2008 (page 9), and on 27 November 2007 (page 12), begins in column 7, at line 53, and states that

> RNA *containing* a nucleotide sequences (sic) identical to a portion of the target gene are preferred for inhibition... (continuing at line 64) Greater than 90% sequence identity or even 100% sequence identity, between the inhibitory RNA and the *portion* of the target gene is preferred. Alternatively, the duplex *region* of the RNA may be defined functionally as a nucleotide sequence that is capable of hybridizing with a portion of a target gene transcript (followed by conditions). The length of the identical nucleotide sequences may be at least 25, 50, 100, 200, 300 or 400 bases.

When read with care, this disclosure clearly does not say that the length of the RNA molecule itself can be as short as 25 bases, only that "the length of the identical nucleotide sequences" contained within such RNA molecules must be "at least 25" or more nucleotides.

The minimum length of the actual RNA molecules is not specified anywhere in the Fire disclosure. An RNA molecule of 1,000 bases would come within the scope of the Fire teaching, so long as a portion of that 1,000 bases included at least 25 nucleotides which have an identical nucleotide sequence to a portion of the target gene transcript to which the molecule could then hybridize by virtue of the at least 25 identical nucleotides. And according to Fire, if a molecule of 1,000 nucleotides were used, it would be highly desirable for the identical sequence length to be much longer than 25 nucleotides, *i.e.*, 100, 200, 300 or 400 bases as noted above.

The number 25 is repeated in Fire's claims, and appellants understand this to be an element in the Examiner's position. Claim 1, directed to a method to inhibit expression of a target gene, employs RNA as a double-stranded molecule with a first strand "consisting essentially of" a ribonucleotide sequence which corresponds to a nucleotide sequence of the target gene and a second strand "consisting essentially of" a ribonucleotide sequence which is complementary to the

nucleotide sequence of a target gene. Clearly, the "consisting essentially of" language refers to the "business" portion of the RNA, not to its total length. This is confirmed by claim 10 which states that the first nucleotide sequence (not strand) comprises "at least 25 bases" which correspond to the target gene and a second nucleotide sequence (not strand) comprises at least 25 bases which are complementary to the nucleotide sequence of the target gene. (The open language of claim 10 clearly indicates that even the first nucleotide sequence may contain additional nucleotides as, of course, can the strand.) The "consisting essentially of" language in claim 1 refers only to the portion of the RNA that is essential for its activity – *i.e.*, the bases that correspond to, or are complementary to, the target gene, as confirmed by *P.P.G. Industries v. Guardian Industries Corp.*, 156 F3d 1351, 48 USPQ2d 1351 (Fed. Cir. 1998).

P.P.G. Industries v. Guardian Industries Corp., 156 F3d 1351, 48 USPQ2d 1351 (Fed. Cir. 1998) is the most frequently cited case with regard to the meaning of "consisting essentially of."

> "Consisting essentially of" is a transition phrase commonly used to signal a partially open claim in a patent. ...by using the term "consisting essentially of" the drafter signals that the invention necessarily includes the listed ingredients and is open to unlisted ingredients that do not materially effect the basic and novel properties of the invention. A "consisting essentially of" claim occupies a middle ground between closed claims...and fully open claims...

This general definition has been cited repeatedly, for example, in *AK Steel Corp. v. Sollac*, 344 F3d 1234, 1239, 1240, 68 USPQ2d 1280 (Fed. Cir. 2003) and in *W. E. Hall Co. v. Atlanta Corrugating LLC*, 370 F3d 1343, 1352, 71 USPQ2d 1135 (Fed. Cir. 2004).

Thus, the "consisting essentially of" language does not imply a limitation on the minimum length of the RNA molecule, only a limitation on the minimum length of the portion that corresponds to the gene to be silenced.

A review of the prosecution history of the Fire patent supports this claim interpretation. It is apparent from this history that "consisting essentially of" was language inserted in the claims in order to distinguish the claimed subject matter from a reference (Agrawal) that disclosed hairpin single-stranded DNA that contained complementary sequences. As Fire's representative argued on page 12 of a Response to an Office action dated 8 January 2002,

> Applicants note that the claims have been amended to refer to the use of double-stranded RNA's *consisting essentially of* two separate strands that are hybridized together. Agrawal discloses only single-stranded polynucleotides that are self-complementary and fold back onto themselves, thereby forming a loop or hairpin that protects the single-strand from degradation. In this regard, the hairpin or loop in the RNA constructs of Agrawal is *essential to* confer the enhanced stability. Thus, Agrawal fails to teach a structure *consisting essentially of* two complementary strands. (Emphasis added.)

Prior to the amendment, the claim had read on sequences "comprising" 25 nucleotides of sequence identity to the relevant gene, and was rejected over the hairpin structures of Agrawal. Thus, the "consisting essentially of" language does not refer to the overall length of the molecule, but rather the absence of a loop connecting two strands.

Appellants have no quarrel that "comprising" language is justified by the specification, but the "consisting essentially of" cannot, and indeed should not, be interpreted to imply an overall length of this size, as this language was introduced specifically to denote the absence of a loop to distinguish Agrawal. The semi-closed language does not relate to the overall length of the RNA strands.

This interpretation of Fire's claims is entirely in consonance with the disclosure in the specification as required by *Phillips v. AWH Corp.*, 415 F3d 1303, 75 USPQ2d 1321 (Fed. Cir. *en banc* 2005). There is no suggestion in the text of Fire that the length of an RNA molecule to be

used in silencing is as short as 25 nucleotides. The plain language of Fire states that it is only the "length of the identical nucleotide sequence" that is supposed to be of this length, and there is no teaching in Fire of the minimum length of the duplex RNA molecules themselves.

If the claims as issued in Fire are to be considered a basis for rejecting the instant claims for anticipation, then it is critical for the Board to recognize that as initially filed, the only mention of a nucleotide length in any of the Fire claims was in dependent claim 10, which read: "The method of claim 1 in which the identical nucleotide sequence is at least 50 bases in length." This language is consistent with what is taught in the Fire specification, as it is drafted in terms of the length of the identical nucleotide sequence, rather than in terms of the minimum length of the molecule containing such sequence.

Claim 1 as filed, from which claim 10 depended, made no mention of size whatsoever:

> A method to inhibit expression of a target gene in a cell comprising introduction of a ribonucleic acid (RNA) into the cell in an amount sufficient to inhibit expression of the target gene, wherein the RNA comprises a double-stranded structure with an identical nucleotide sequence as compared to a portion of the target gene.

Only in December 2000, well after the priority and actual filing date of the instant application and more than a year after the publication of the seminal Baulcombe and Hamilton *Science* article of October 1999 disclosing short RNA molecules of 25 ± 5 nucleotides in length as associated with PTGS, for the first time, claims were introduced into the Fire application reciting a 25 nucleotide element. Even then, this was explicitly stated in terms consistent with the teaching in the specification, *i.e.*, as "an identical nucleotide sequence as compared to a portion of a target gene of at least 25 bases in length" (see claims 1, 22, 39 and new claim 40 introduced in the December 2000 Fire response). Claim 1 as amended in December 2000 read:

> A method to inhibit expression of a target gene in a cell comprising introduction of a ribonucleic acid (RNA) into the cell in an amount sufficient to inhibit expression of the target gene, wherein the RNA comprises a double-stranded structure with an identical nucleotide sequence as compared to a portion of the target gene **of at least 25 bases in length**. (New text added to the claim is bolded.)

The first date on which a claim was introduced into the Fire application in which a claim reaches an RNA molecule that comprises a sequence at least 25 nucleotides in length is in the Fire response dated August 14, 2001, where, for the first time, for example in claim 1, the method is recited as a method for inhibition of expression by

> [I]ntroduction of a ribonucleic acid (RNA) into the cell ...wherein the RNA comprises a double-stranded structure having a first ribonucleotide sequence comprising at least 25 bases which correspond to a nucleotide sequence of a target gene and a second ribonucleic acid sequence comprising at least 25 bases which are complementary to the nucleotide sequence of a target gene.

This is still consistent with the specification and still does not imply that the RNA molecules themselves could be only 25 nucleotides long.

As noted above, the claims could only be read to imply a teaching of RNA molecules that are themselves 25 nucleotides in total length after the "consisting essentially of" language was added to claim 1 in the Response filed 8 January 2002 and the 25 nucleotide limitation moved to claim 10 in that Response. As noted above, however, the explanation provided by the applicant for adding this language made it clear that it was intended simply to exclude the putatively "essential" loops that are disclosed in the Agrawal document.

Thus, if the claims of Fire are properly read, either there is no implication that RNA molecules themselves as short as 25 nucleotides are suggested, or such a suggestion must clearly be considered new matter since Fire's specification itself does not support such an interpretation. Such

new matter, of course, is accorded only the date of 8 January 2002 and thus is not properly cited against the claims of the present appellants.

Even if Fire had disclosed that RNA molecules used in PTGS could be as short as 25 nucleotides, Fire itself mandates that length as an absolute minimum, and Graham does not suggest that the "molecules" of Fire be shortened further. Graham teaches away from this by suggesting only that the structural gene components (DNA of his constructs, not the RNA produced by them) contain anywhere from 20 to the exemplified 1,385 nucleotides in each strand. As supported by *Baird* and *Atofina*, suggestion of such a large genus hardly suggests the 20-24 nucleotide RNA (not DNA) species that is required by the claims presented on appeal. Further, as discussed above, the mention in Graham of a construct component of 20-30 nucleotides in length does not teach that this is the total size of the construct sequence that is transcribed, or that the RNA that is transcribed is of that length.

Viewed objectively, Fire and Graham relate respectively to RNA molecules and DNA constructs which produce RNA molecules that are substantially larger than the 20-24 nucleotides that are specifically required by the present claims.

One last observation with regard to the combination of Fire and Graham (or either, alone) is that neither document specifically suggests short RNA molecules as a particular embodiment even in light of the known interferon problem described and documented by appellants in the Response mailed 28 September 2008. Had it been appreciated by either Graham or Fire that such molecules are in fact the effectors of PTGS, surely they would have at least mentioned that it would be desirable either to produce or to use molecules in that size class – this is not found in either of the cited documents.

The Examiner's response in the Advisory Action mailed 4 November 2008 to this argument is to state that the interferon response occurs only in vertebrates and not in plants, which is the subject matter elected in the present case. This argument is entirely spurious. The issue is what Graham and Fire disclose, not what is being prosecuted here. Fire exemplified nematodes, and Graham exemplified constructs of particular genes in a mammalian system, and both disclosures encompass vertebrate systems. See, *e.g.*, Fire at column 4, lines 62-65, column 8, lines 12-19, and column 9, lines 65, *et seq.*, and Graham at column 2, lines 56-58, and column 14, lines 48-54. One would expect that the concern over induction of an interferon response by long-dsRNA would have led Fire and Graham to disclose the preference for short RNA molecules had they had any appreciation of the utility of such molecules for inducing PTGS. Appellants' election is simply irrelevant with respect to what either Fire or Graham does or does not disclose.

Finally, in response to appellants' argument that Graham, at best, teaches intracellular production of RNA molecules whereas Fire's comments regarding length apply to externally administered RNA, the documents thus effectively describing apples and oranges, the Examiner simply says that there is no reason to think that the criteria for success would be any different in each case. But there is a reason. RNA obtained from constructs would be generated in the nucleus and processed prior to entering the cytoplasm. Externally administered RNA, on the other hand, is sent directly to the cytoplasm, avoiding any such nuclear processing steps. In addition, the RNA externally provided would not necessarily contain any transcription-generated signals that are relevant to translation, such as translation termination signals and polyA sequences, as could be generated by constructs designed to generate RNA without regard to production of a specific, small, size-class of molecules as called for in the instant application and claims. For these reasons, the

discussion of the requirements for a construct, in terms of length, is by no means applicable to externally supplied RNA. There is, therefore, no basis for thinking that whatever Graham might suggest in terms of size of structural gene components would have anything to do with the size of RNA molecules of Fire.

The bellwether case for evaluating obviousness based on a combination of documents is *KSR International v. Teleflex, Inc.*, 82 USPQ2d 1385 (S. Ct. 2007). It is pertinent with respect to this last point. While the subject matter in that case is quite different from that herein, it is relevant that the Supreme Court in *KSR* essentially affirmed that the law to be applied in evaluating obviousness is that enunciated in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). One is to determine the scope and contents of the prior art; determine the differences between the prior art and the claims at issue; resolve the level of ordinary skill in the pertinent art, and, on the basis of these inquiries, decide whether the identified differences would or would not have been obvious to this person of ordinary skill. A *prima facie* case of obviousness is made out only if these differences would have been obvious to such a person. This purports to be an objective test.

In order to find obviousness by combining the teachings of two documents, there has to be some reason to combine them. In *KSR*, there was a reason to combine a document that described everything about the patented gas pedal except the inclusion of a sensor rather than a mechanical mechanism to drive the pedal. Since electronic sensors in the context of gas pedals were already disclosed in the art, the Court found that it was obvious to employ such a sensor in the prior art gas pedals.

In the present case, there is no reason to combine the teachings of Fire with those of Graham because Graham is exclusively concerned with providing synthetic genes that are "capable of

modifying the expression of a target gene in a cell, tissue or organ, ...". It is completely unclear as to what kind of a mechanism is envisioned by Graham, but it is clear that Graham is not focused on post-transcriptional gene silencing. The only mention in the entire Graham disclosure of post-transcriptional gene silencing is in the references cited, and in the Background of the Invention section of the patent, column 1, lines 29-36, it is stated: "Current methods for downregulating gene expression using recombinant DNA technology comprise the introduction of a transgene to the cell which is capable of repressing expression of an endogenous target gene, either transcriptionally or post-transcriptionally. **However, the precise mechanism is not known.** Moreover, the efficiency of current approaches is low and the results are variable and unpredictable." Thus, Graham is actually aimed at improving the known methods of using recombinant DNA technology by introducing a transgene of a particular arrangement into a cell, such that the transgene is capable, by some means admittedly unknown to Graham of repressing expression of an endogenous target gene. Graham is silent on everything except the nature of the synthetic gene.

Graham states in column 11, at lines 17, *et seq.*, that in a particularly preferred embodiment, the multiple structural gene unit comprises two identical or substantially identical structural genes comprising nucleotide sequences derived from the BEV polymerase or tyrosinase gene or homolog, analog or derivative thereof placed in a head-to-head or head-to-tail configuration. Since the constructs designed to produce dsRNA taught by Fire to be required to induce PTGS would require a head-to-head configuration (or tail-to-tail), the alternative presented by Graham on equal footing (a head-to-tail configuration) further demonstrates that either PTGS is not the focus of Graham's teaching and/or that Graham did not understand how to generate the actual effectors of gene silencing, (either the long dsRNA of Fire or the short RNA molecules, SRMs, of the present

invention). Graham is not even limited to generating RNA – in column 11, Graham envisions that "if the multiple structural gene or any individual structural gene thereof is intended to be both transcribed and translated, a translation start signal may be included… ." The silencing, evidently, could involve the protein produced by the synthetic genes. This is reinforced in column 12, where the applicant discusses "stuffer fragments" which permit detection of the proteins expressed from the synthetic gene. See, for example, column 12, lines 9-13.

Fire, on the other hand, concerns only providing double-stranded RNA specifically to effect inhibition of expression (column 6, lines 33-43). There is no suggestion that any protein derived from the dsRNA would have any role; indeed, dsRNA would presumably not be translated into protein in any event.

The question then becomes, would the skilled artisan be motivated to look to Graham to see if the double-stranded RNA's described by Fire could be shortened. The answer is no, since Graham never discusses RNA at all, and in relation to palindromic constructs, discusses the danger of forming hairpin loops which can recombine *in vivo*. Thus, any RNA that might be produced by Graham's constructs, including any double-stranded RNA, would be considered an unwanted side effect for one of the Graham embodiments (see column 10, lines 26-44).

Objectively viewed, then, the differences between the scope and content of the cited prior art and the invention claimed in this application would not have been obvious to the ordinary skilled practitioner. This is evidenced by the award of both the Lasker Prize and the Franklin Medal to Dr. Baulcombe for exactly this work. Clearly, those of ordinary skill did not think that the contribution of the present invention was obvious.

The entire predicate of the Examiner's rejection is based on the fallacious notion that Fire teaches that double-stranded DNA molecules of only 25 nucleotides would be effective in silencing genes by PTGS, and the false assumption that Graham teaches that RNA molecules as short as 20-24 molecules could be used. Neither is true. As demonstrated above, there is no suggestion in either document that RNA molecules as short as those claimed could be effective.

It is also significant that the claimed invention is based, not on manipulating any prior art documents, but rather on a pristine finding based on appellants' own work that in every instance where post-transcriptional gene silencing, there was an invariant correlation with the presence of the short RNA molecules. These, the present inventors discovered, are the actual effectors of post-transcriptional gene silencing, and this finding has since been universally affirmed in the literature. This is not at all analogous to instances where obviousness is found based on combining the actual disclosures of two separate documents.

In summary, therefore, as discussed above, it is urged that the rejection of claims 116-124 as obvious in light of Fire in combination with Graham is in error for at least the following reasons:

1. Fire does not in fact teach RNA **molecules** of as few as 25 nucleotides as asserted by the Examiner;
2. The Examiner's reading of the Fire claims is not supported by the teaching in the specification or by the prosecution history;
3. If the claims in Fire are interpreted as the Examiner suggests, they contain new matter entitled only to a date after the priority date and actual filing date of the instant application, and therefore may not properly be relied on as prior art at all;
4. Even if Fire could be read as teaching RNA **molecules** of at least 25 nucleotides in length, Fire teaches 25 nucleotides as an absolute minimum and there is nothing in Graham that can or should properly be relied on as teaching an RNA **molecule** smaller than 25

nucleotides in length, thus leaving even the broadest interpretation of what is asserted by the Examiner as being taught by Graham in combination with Fire outside the size range of RNA molecules claimed in the instant application;

5. The failure of either Fire or Graham to specifically teach the benefits of using RNA molecules in the size range claimed in this application, in spite of the known problem of induction of the non-specific interferon response when using long dsRNA molecules, is strong evidence that neither Fire nor Graham appreciated that molecules in the size class claimed in the present application could be used to effect PTGS.

6. Appellants had neither the motivation to combine the teachings of Graham with those of Fire, nor, had they done so, would they have arrived at the invention disclosed and claimed in the present application. Instead, they independently discovered the effectors of this process and how to use them for this purpose. The reference point in this case is empirical evidence, not an hypothetical reconstruction based on documents reporting the work of others. This is entirely different from the kind of reference mining that undermined patentability in *KSR*.

C. The Rejection of all Claims as Assertedly Obvious Over Brown Requires the Insertion of the Teaching of the Present Application into What Brown Discloses.

Brown is concerned generally with regulating gene expression of products of the gibberellin biosynthetic pathway. Various methods of suppressing expression are referred to, and summarized in column 3, lines 49-67. Among these are antisense constructs, ribozymes, triplex DNA and "cosuppression." Antisense, ribozyme and cosuppression are described in detail beginning in column 54, at line 44, and Brown there essentially provides a discussion of the prior art in these methods that continues to column 57, line 46. In describing cosuppression, Brown states "overexpression of mRNA's involved with GA synthesis could be used to decrease GA levels" (column 56, lines 37, *et seq.*). Brown goes on to state that cosuppression is also known as "co-sense

suppression, homology dependent gene silencing, repeat-induced gene silencing, etc.," and is "the inactivation of a gene in a cell where it is normally functional." The first review article cited is authored by none other than Dr. Baulcombe in 1996. As Dr. Baulcombe is a co-inventor in the present case with a filing date in 1999, appellants are certain this review does not describe short RNA sequences. It is certainly not stated in Brown that "cosuppression" requires both sense and antisense RNA.

The only mention of any sequence length for any component of a silencing method is in column 3, at line 63, which clearly refers to silencing "by antisense expression of a sequence that comprises at least 12 contiguous nucleotides (and preferably at least 15, 18, 20, 24, 30, 40 or longer up to and including the entire length of) SEQ ID NO:1, 2, 3, 4, 5, 6 or 8 or complements thereof."

Three observations are pertinent. Brown refers to sequences or their complements. The present invention requires the presence of both sense and antisense short RNA molecules, not sense or antisense in the alternative. Thus, the noted section of Brown clearly does not refer to the methods claimed in this case. There is no teaching of methods of any type of gene silencing involving both sense and antisense RNA or generating both a sense and antisense RNA.

Second, like Graham, the numbers recited by Brown recite the DNA sequence to be expressed, not the RNA sequence to be produced. As was the case with Graham, the expression will occur in the nucleus and thus accoutrements of nuclear production of the RNA, including providing translation termination signaling, for example, and processing that might take place in the transition from the nucleus to the cytoplasm renders this inapplicable, at least to claims 116-124.

Third, the suggestion of enormous range between 12 nucleotides and a full-length reading frame does not suggest the specific 20-24 nucleotide RNA's required by the claims.

It is difficult for appellants to understand how Brown could possibly be read to suggest the claims of the present invention without the claims of the present invention being placed in front of the reader. It appears that the invention claims have been used as a guide to impose an interpretation on the disclosure of Brown that is actually not present. This, of course, is not permissible.

D. All of the Foregoing Rejections Lose Sight of the Acknowledged Contribution of Present Appellants to the Gene Silencing Technology.

Because of the work of the present appellants, it is now understood that the mechanism of post-transcriptional gene silencing specifically involves short RNA molecules of 20-30 nucleotides in length (only molecules in the 20-24 nucleotides size range are claimed in the present application) both short sense RNA molecules and short antisense molecules being present. Prior to appellants' invention, there was no understanding in the art that this was the case. The cited portions of Graham, Fire and Brown all represent disclosures of wide ranges of sizes that are putatively operable, even if these documents were interpreted to discuss production of RNA molecules that could include the size range claimed in the present application. In fact, none of them do. Graham describes only DNA constructs to which the range of numbers disclosed by Graham apply, not to the RNA molecules produced. Fire refers only to regions of complementarity and correspondence to the target gene in larger RNA molecules to which the enumerated sizes apply. Brown specifies only this range of sizes as it applies to DNA constructs which, by Brown's own terms, contain the stated number of nucleotides in either the antisense **or** sense direction for expression, not both, as required by the claims. In short, with respect, appellants believe that the Examiner is reading the

teachings of the present invention into the disclosures of the cited documents. For these reasons, the rejections of the pending claims should be reversed and all claims be passed to issue. Appellants respectfully request the Board to take this action.

8. Claims Appendix

An Appendix containing a copy of the claims as currently pending is attached.

9. Evidence Appendix

1. Reports of the Lasker Awards
2. Reports of the Franklin Medal
3. Three journal articles verifying the accuracy of appellants' characterization of the art as disclosing interferon interference from long RNA sequences.
4. Responses filed in the prosecution of Fire, US 6,506,559.
5. The Baulcombe and Hamilton 1999 *Science* article.

All of documents 1-3 were submitted with the Response mailed 29 September 2008 to final Rejection. Document 4 is inherent in the '559 patent made the basis for rejection. The *Science* article is of record in the prosecution of the instant application.

10. Related Proceedings Appendix

There are no decisions rendered by the Court or Board in any proceeding identified in section 2 above, therefore no Appendix is included.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to **Deposit Account No. 03-1952**.

Respectfully submitted,

Dated: March 6, 2009

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CLAIMS APPENDIX

1-115. (canceled)

116. (previously presented): A method of silencing a gene in cells by post-transcriptional gene silencing (PTGS) which method comprises introducing into said cells a composition that contains short RNA molecules (SRMs),

which SRMs are isolated short sense RNA molecules (SSRMs) and isolated short antisense RNA molecules (SARMs) at the same abundance;

wherein said SARMs are complementary to a region of a target RNA transcribed from a gene which is silenced when said short RNA molecules are present in cells containing said gene and said SSRMs correspond to said target RNA; and

wherein the SSRMs and SARMs consist of 20, 21, 22, 23 or 24 nucleotides,

whereby said gene is silenced.

117. (previously presented): The method of claim 116, wherein the cells are contained in an organism and said introducing comprises administering said SRMs to the organism.

118. (previously presented): The method of claim 116, wherein the SRMs are synthetic.

119. (previously presented): The method of claim 116, wherein the SARMs have a structure complementary to a target mRNA transcribed from a gene endogenous to a plant, a mammal, an avian organism, a reptile, an insect, a protozoan, a nematode, or a virus.

120. (previously presented): A method of silencing a gene in cells of an organism by post-transcriptional gene silencing (PTGS) which method comprises introducing into said cells a composition that contains isolated short antisense RNA molecules (SARMs) and isolated short sense RNA molecules (SSRMs) corresponding to a target RNA transcribed from said gene, the nucleotide sequences of which consist of 20, 21, 22, 23 or 24 nucleotides and wherein said SARMs can base pair with said target RNA.

121. (previously presented): The method of claim 120, wherein said SARMs and SSRMs are present at the same abundance.

122. (previously presented): The method of claim 120, wherein the cells are contained in an organism and said introducing comprises administering said SSRMs and SARMs to the organism.

123. (previously presented): The method of claim 120, wherein the SSRMs and SARMs are synthetic.

124. (previously presented): The method of claim 120, wherein the SARMs have a sequence that can base pair to a target mRNA transcribed from a gene endogenous to a plant, a mammal, an avian organism, a reptile, an insect, a protozoan, and a nematode, or a virus.

125. (previously presented): A method of silencing a gene in cells by post-transcriptional gene silencing (PTGS) which method comprises introducing into said cells a composition that contains at least one vector that, when introduced into said cells, produces short RNA molecules (SRMs),

which SRMs are short sense RNA molecules (SSRMs) and short antisense RNA molecules (SARMs);

wherein said SARMs are complementary to a region of a target RNA transcribed from a gene which is silenced when said short RNA molecules are present in cells containing said gene and said SSRMs correspond to said target RNA; and

wherein the SSRMs and SARMs consist of 20, 21, 22, 23 or 24 nucleotides,

whereby said gene is silenced.

126. (previously presented): The method of claim 125, wherein the cells are contained in an organism and said introducing comprises administering said composition to the organism.

127. (previously presented): The method of claim 125, wherein the SARMs have a structure complementary to a target mRNA transcribed from a gene endogenous to a plant, a mammal, an avian organism, a reptile, an insect, a protozoan, a nematode, or a virus.

128. (previously presented): A method of silencing a gene in cells of an organism by post-transcriptional gene silencing (PTGS) which method comprises introducing into said cells a composition that contains at least one vector that, when introduced into said cells, produces short antisense RNA molecules (SARMs) and short sense RNA molecules (SSRMs) corresponding to a target RNA transcribed from said gene, the nucleotide sequences of which consist of 20, 21, 22, 23 or 24 nucleotides and wherein said SARMs can base pair with said target RNA.

129. (previously presented): The method of claim 128, wherein the cells are contained in an organism and said introducing comprises administering said composition to the organism.

130. (previously presented): The method of claim 128, wherein the SARMs have a sequence that can base pair to a target mRNA transcribed from a gene endogenous to a plant, a mammal, an avian organism, a reptile, an insect, a protozoan, a nematode, or a virus.

EVIDENCE APPENDIX

This appendix contains the following evidentiary material already of record:

1. Reports of the Lasker Awards
2. Reports of the Franklin Medal
3. Three journal articles verifying the accuracy of appellants' characterization of the art as disclosing interferon interference from long RNA sequences:

   Tuschl, T., *et al., Genes & Dev.* (1999) 13:3191-3197

   Zamore, P. D., *Cell* (2000) 101:25-33

   Elbashir, S. M., *et al., Nature* (2001) 411:494-498
4. Responses from prosecution of Fire, US 6,506,559
5. The Baulcombe and Hamilton 1999 *Science* article.

All of documents 1-3 were submitted with the Response mailed 29 September 2008. Document 4 is inherent in the '559 patent made the basis for rejection. The *Science* article is of record in the prosecution of the instant application.